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Clinical Characteristics of Small Functioning Adrenocortical Tumors in Children

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Twenty of 67 children registered on the International Registry of Childhood Adrenocortical Tumors between May 1988 and December 1994 had small adrenocortical tumors (defined for this study as measuring $\leqslant$ 200 cm^3 and/or weighing $\leqslant$ 100 g). We reviewed the records of these 20 patients to characterize the clinical and pathologic findings and outcomes of children with small adrenocortical tumors. Median patient age was 2 years (range, 4 months to 5 years). There was only one boy. All had clinical signs of virilization, and seven had signs or symptoms of Cushing syndrome. A median 5.5 months (range, 1–40 months) had elapsed between the first signs of endocrine dysfunction and diagnosis. All tumors were surgically resected. Tumor volume was 3.3–195 cm^3 (median, 38.7 cm^3), and weight was 3.7–100 g (median, 36 g). Tumor samples were histologically reviewed in 18 cases. Eight were adenomas, and 10 were carcinomas (6 low grade and 4 high grade). Pathology records described tumor with diagnostic features of adrenocortical carcinoma in two patients. One patient received mitotane for 8 months after surgery. Only one patient had recurrent disease, which was detected 6 months after diagnosis and proved rapidly fatal. Another has been lost to follow-up. The remaining 18 patients are alive with no evidence of disease at a median 2.3 years (range, 6 months to 6.1 years) after diagnosis. Our data suggest that children with small adrenocortical tumors have an excellent prognosis with surgery as the sole therapy, regardless of tumor histiotype. **Med. Pediatr. Oncol. 28:175–178.**

Key words: childhood adrenocortical carcinoma; prognostic factors; treatment

INTRODUCTION

Adrenocortical neoplasms are rare in children [1]. Carcinoma is considered the most common histiotype among this heterogeneous group of tumors [2], but because of the difficulty of distinguishing adrenocortical adenoma from carcinoma [3], not all cases are recorded and the actual incidence is uncertain. Recently published data indicate that adrenocortical carcinoma comprises approximately 0.2% of all childhood cancers [1]. Its rarity has hindered the identification of meaningful prognostic factors. Tumor size [4–7], age [8], histiotype [3,9,10], hormonal secretion [5,8], DNA ploidy [11,12], and other clinical, surgical, and laboratory parameters [3–6,13] are reportedly associated with outcome, but findings are inconsistent. In a retrospective study of 40 surgically treated cases from a single institution [5], tumor size was significantly associated with prognosis, and a later analysis showed that patients with carcinoma histiotype had significantly poorer outcomes than did those with adenoma [9]. We report 20 patients with small adrenocortical tumors registered in the International Registry of Childhood Adrenocortical Tumors (IRCAT).

PATIENTS AND METHODS

From May 1988 to December 1994, 67 children with adrenocortical tumors were registered on the IRCAT, a voluntary registry including but not confined to the United States, Brazil, Canada, Uruguay, Norway, Iceland, and Chile. All patients were enrolled on the same treatment protocol. Patients with small tumors (measuring $\leqslant$ 200 cm^3 and/or weighing $\leqslant$ 100 g) were treated with surgery alone, whereas patients with larger tumors were treated with adjuvant mitotane therapy. These cut-off values were based on the findings of a previous study [5]. This study focused on the small tumor group. The larger tumors and their response to treatment will be the subject of another report.

Diagnosis was made on the basis of the gross and histologic appearance of tissue obtained at surgery. Tumor samples from 18 patients were reviewed and classified by one pathologist (M.F.B.) using previously reported histologic criteria [9]. Pathology records describing tumor

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with diagnostic features of adrenocortical carcinoma were available for two patients. The volume and weight of each tumor were obtained from pathology reports. The tumor volume was calculated by multiplying width × length × height. The weight was obtained using a calibrated scale. Assays of serum or urinary adrenal hormones and their metabolites were performed using commercially available reagents. A patient was considered to have Cushing syndrome if he or she had clinical signs such as moon facies, weight gain, centripetal distribution of fat (abdomen and upper dorsal region), plethora, hypertension, striae plus elevated serum cortisol, or high 24-hour urinary excretion levels of 17- hydroxycorticosteroids [14]. Patients with clinical or laboratory features of both Cushing syndrome and virilization (premature appearance of pubic hair plus clitorimegaly or phallomegaly) were designated as having mixed-type tumors.

Every patient had surgical tumor resection. One patient, whose tumor spilled into the peritoneal cavity during surgery, received mitotane (1,1 dichloro-2-[O-chlorophenyl]-2-[p-chlorophenyl]- ethane) postoperatively.

RESULTS

Table I shows selected clinical, pathologic, and outcome features of patients with small adrenocortical tumors. Only Patient 16 was a boy. The median age was 2 years (range, 4 months to 4.8 years). Signs of virilization were present in every child. Seven patients had clinical or laboratory findings of Cushing syndrome in addition to virilization. The median interval between the first symptoms and the diagnosis of adrenocortical tumor was 5.5 months (range, 1–40 months). The median tumor volume was 38.7 cm^3 (range, 3.3–195 cm^3), and the median tumor weight was 36 g (range, 3.7–100 g). Eight tumors were classified as adenomas, and 12 were classified as carcinomas. Of the tumor samples available from 10 patients with carcinomas, 6 had low-grade and 4 had high-grade histology.

Tumors were considered completely excised in all patients. Patient 9 received mitotane for 8 months at the discretion of the attending physician due to concerns about tumor contamination of the peritoneal cavity. At a median follow-up of 2.3 years (range, 0.5–6.1 years), 18 patients remained alive and free of disease (Fig. 1). One patient developed pulmonary metastasis 6 months after diagnosis and died of progressive disease shortly thereafter. One patient, who had been previously diagnosed with choroid plexus carcinoma, has been lost to follow-up.

DISCUSSION

In this relatively large group of children with small adrenocortical tumors, surgery alone was usually sufficient for successful management, regardless of tumor histology. These findings support our previous observations and those of other investigators that small adrenocortical tumors are associated with good prognosis [7,9].

If tumor size is to be used as a prognostic indicator and a staging criterion in childhood adrenocortical tumors, a reliable method of tumor measurement is needed. Due to shape irregularity, measuring tumors in their three diameters with a ruler may be misleading. In addition, although tumors are routinely weighed in pathologic examinations, tumor adherence to normal structures can cause spurious results. Tumor size estimation can possibly be improved by imaging studies [4] or by adjusting tumor size to body surface area [15,16]. Despite the obstacles to accurate measurement, however, patients with small adrenocortical tumors, as defined in this study, appear to have an excellent prognosis.

The histologic classification of endocrine neoplasias, particularly of childhood adrenocortical tumors, is very difficult [3]. Adrenal tumors are classified as adenomas or carcinomas based on their cytologic abnormalities [10,17]. However, in addition to the morphologic aspect, some investigators also consider tumor weight, presence of metastasis at presentation, and/or outcome in retrospectively establishing the histologic grade [6]. A previous report of ours [9] suggested that both tumor weight and histology are associated with outcome. In that study, in which the pathologists were blinded to tumor size, clinical characteristics, and outcome, prognosis was significantly better in patients with adenoma histology than in patients with either low-grade or high- grade carcinoma. The present study extends these observations to indicate that patients with small tumors probably have very good prognosis regardless of the histiotype.

The clinical demographics of the patients in this study are intriguing. All patients except one were female, all were younger than 5 years of age at diagnosis (median age, 2 years), and adenoma histology was frequent (40%). In contrast, in our unselected series of 40 childhood adrenocortical tumors from a single institution, the median age at diagnosis was 3.9 years, the female:male ratio was 2.3:1, and the frequency of adenoma histology was less than 15% [5]. In a review of 92 pediatric adrenocortical tumors from several institutions, Humphrey et al. [8] found a 2.1:1 female:male ratio and a 22% frequency of adenoma. Although it was not emphasized in their review, among 20 patients with small adrenocortical carcinomas $\leqslant$ 160 g, 15 (75%) were 4 years of age or younger (only two patients were older that 8 years of age) and 12 (60%) were female. In that review, the authors proposed that adrenocortical carcinoma is two diseases with different age distributions: an "infantile" type composed of patients 7 years of age and younger who have a good prognosis, and an "adolescent type" associated with dismal prognosis [8]. However, there was a large range of tumor weights ($<$ 20 to $>$ 800 g) among patients in the infantile group. When tumor weight is considered, a significant difference in survival emerges within this age group; 74% of patients with small tumors ($\leqslant$ 160 g) were alive at the time of publication, compared with only 36% of those with larger

TABLE I. Selected Pathologic and Clinical Features of 20 Children With Small Adrenocortical Tumors

Patient #	Age	Interval* (months)	Clinical Type	Tumor Volume (cm^3)	Tumor Weight (g)	Histology Grade	Survival (months)
1	1	8	Mixed	72	42	ACC-low	74
2	3.3	27	Viril.	8	3.7	Adenoma	57
3	4	1	Mixed	38.7	30	ACC-high	58
4	1.9	6	Mixed	50	36	ACC-low	1
5	2.7	18	Viril.	9	6	Adenoma	46
6	0.9	1	Viril.	63.8	44	ACC-high	32
7	1.6	10	Viril.	181	90	Adenoma	44
8	0.9	4	Viril.	3.3	10	Adenoma	25
9†	1.3	3	Mixed	121	60	ACC-low	44
10‡	3.5	40	Mixed	NA	60	ACC-nos	6
11	4	7	Viril.	40.5	40	ACC-low	19
12	1.8	4	Viril.	31.5	19	ACC-low	22
13	3.2	5	Viril.	11.5	8	ACC-high	33
14	2.6	6	Viril.	31.5	100	Adenoma	31
15	1.7	6	Mixed	107	NA	Adenoma	31
16	4.8	12	Viril.	26.2	15	Adenoma	19
17	2	3	Viril.	195	100	ACC-high	17
18	0.3	1	Viril.	95	100	ACC-low	14
19	0.8	5	Viril.	34	32	ACC-nos	7
20	3.5	2	Mixed	33	15	Adenoma	9

*Interval between symptom/sign onset and diagnosis. †Patient treated with 8 months of mitotane postoperatively. ‡Patient with lung metastasis. NA: Not available; nos: Not otherwise specified.
Mixed = Cushing + Virilization; Viril. = Virilization; ACC = Adrenocortical carcinoma; high = high grade; low = low grade; nos = not otherwise specified.

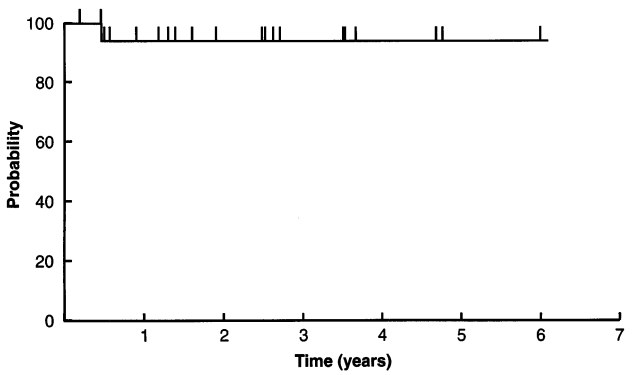

Fig. 1. Overall survival of 20 patients with small functioning adrenocortical tumors. One patient was lost to follow-up.

tumors. Therefore, we suggest that very young virilized females with small tumors have an excellent outcome and comprise a more homogenous group in terms of clinical presentation and prognosis.

The molecular genetics of adrenocortical tumors are coming to light slowly. Some patients have germline p53 mutations (Li- Fraumeni syndrome) [3,18–20], and others have abnormalities of the 11p15 region (Wiedemann-Beckwith syndrome) [3]. In some reports, adrenocortical neoplasia was the first manifestation of the Li-Fraumeni familial cancer syndrome in the kindred [19]. At present, it is not known what proportion of patients with small adrenocortical tumors have the germline p53 aberrations and whether they have an increased susceptibility to other neoplasias later in life. In one patient in our series and in several other reported cases, the adrenocortical tumor preceded or followed the development of other tumors [21–24]. Elucidation of the molecular genetics of these tumors will allow early identification of individuals who can benefit from familial genetic counseling and management designed to reduce the likelihood of these other cancers and/or improve the rapidity of diagnosis. Whenever possible, radiotherapy and large doses of alkylating agents should be avoided in patients with germline mutations who require adjuvant therapy.

In summary, our data suggest that children with small adrenocortical tumors (those $\leqslant 200$ cm^3 or $\leqslant 100$ g) have an excellent prognosis despite malignant histologic features.

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